Mini Review
Sciences of Pharmacy

Penicillin Binding Protein Mutation and Beyond: A Comprehensive Approach to Addressing Streptococcus pneumoniae Resistance

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Abstract: Antibiotic resistance is a critical issue that threatens global health. Streptococcus pneumoniae, a common respiratory pathogen, has developed resistance to β-lactam antibiotics, which is of great concern. The primary mechanism of β-lactam resistance in S. pneumoniae is the acquisition of PBP genes from related species through recombination, resulting in changes in penicillin-binding proteins that affect cell wall synthesis. This mini-review summarized the understanding of β-lactam resistance in S. pneumoniae, focusing on the mechanisms and factors influencing resistance development. We conducted a comprehensive literature search using PubMed and Google Scholar, with the keywords 'Resistant Streptococcus pneumonia', 'Mechanism of Streptococcus pneumoniae resistant', and 'Penicillin Resistant on Binding Protein of Streptococcus pneumonia'. Our literature review revealed that the prevalence of β-lactam resistance in S. pneumoniae has increased, leading to treatment failures and mortality rates. In addition to acquiring PBP genes, mutations in other PBP and non-PBP genes can contribute to resistance. Furthermore, S. pneumoniae has intrinsic resistance to various antibiotics, including first-generation polypeptides, aminoglycosides, and quinolones. Our review highlights the importance of understanding the complex mechanisms of β-lactam resistance and the need for continued efforts to monitor and control antibiotic resistance in S. pneumoniae. Further research is needed to explore novel strategies for combating antibiotic resistance in this pathogen.

Introduction

The discovery of penicillin in the first decade of the twentieth century, and all subsequent antibiotics, is undoubtedly one of the most significant triumphs in medicine and pharmacology. Not only have these treatments saved millions of lives, but they are also essential to be used in frequent hospital operations such as general surgery, organ transplantation, dialysis for renal failure, and chemotherapy for cancer, where their capacity to cure secondary infections is critical. Unfortunately, antibiotics' potential to heal infectious illnesses is seriously jeopardized due to the introduction and spread of antibiotic-resistant bacteria (1).

The capacity of microorganisms to resist the action of antimicrobial agents, which happens when antibiotics lose their effectiveness in preventing bacterial growth, is referred to as antibiotic resistance (2, 3). According to the European Center for Disease Prevention and Control (ECDC), around 25,000 Europeans die each year due to resistance, and an extra €1.5 billion is spent on patient care costs (1). According to the Centers for Disease Control and Prevention (CDC), a comparable number of fatalities occur in the United States. The World Health Organization projects that rising antibiotic resistance will cause 10 million deaths by 2050 (4, 5).

Antibiotic resistance has emerged as a severe issue in the medical world. Several factors impact antibiotic resistance, including the increased use of antibiotics in illness treatment. Another concern is the proliferation of antibiotic classes, which will make it simpler for

bacteria to evolve resistance to antibiotics in the future (6). The rise of Streptococcus Pneumonia resistance to β-lactam antibiotics is a particularly concerning kind of antibiotic resistance. Streptococcus pneumonia is a bacteria that has caused millions of fatalities worldwide. These bacteria are general integrants of the human nasopharyngeal microbiota, although they can move and invade sterile tissues and organs. Streptococcus pneumoniae is a leading cause of morbidity and death in lower respiratory tract infections in children under five worldwide. Between 2000 and 2015, 294,000 HIV-uninfected children aged 0 to 59 months died from pneumococci, making pneumonia the most frequent illness (7).

Penicillin receptor binding proteins impact antibiotic resistance in Streptococcus pneumoniae. Penicillin-binding protein has been generally examined and linked to antibiotic resistance in Streptococcus pneumoniae bacteria. As a result, it is critical to understand the role of penicillin-binding protein in antibiotic activity. One of the most effective therapies is the exact identification of changes in the penicillin-binding protein that impact the incidence of antibiotic resistance so that the benefit of the medication may be increased while also preventing broader dissemination. Because of the advent of widespread antibiotic resistance, analysis and study related to this topic are required to establish the kind of antibiotic resistance induced by Streptococcus pneumoniae, as well as precise and accurate detection to limit the impact of Streptococcus pneumoniae resistance. This identification allows further efforts to limit and treat the impact of Streptococcus pneumoniae infection.

Methodology

The method employed in this study was a literature review of several international journals published in PubMed, ScienceDirect, and Google Scholar in the recent ten years (2012-2022). The keywords used were ‘Resistant Streptococcus pneumonia’, ‘Mechanism of Streptococcus pneumoniae resistant’, and ‘Penicillin Resistant on Binding Protein of Streptococcus pneumonia’. The initial number of articles found was 35 articles. The articles were then yielded 13 articles (published from 2012 to 2022) that provided information regarding the prevalence of antibiotic resistance, Streptococcus pneumoniae resistance, and the resistance mechanisms.

Streptococcus pneumoniae and Antibiotics Resistance

It was found that the β-lactam class of antibiotics had the highest level of resistance to Streptococcus pneumoniae (see Table 1). The abuse of β-lactams has contributed to the rise of penicillin-resistant Streptococcus pneumoniae, a problem that persists and is considered a public health issue. Drug-resistant S. pneumoniae is a severe problem in the United States, according to a 2013 study issued by the Centers for Disease Control and Prevention (see Table 1). Antibiotic-resistant Streptococcus pneumoniae strains are estimated to cause more than 1.2 million infections yearly, resulting in more than 7000 fatalities in the United States despite medication availability (8). Penicillin's Minimum Inhibitory Concentration (MIC) has been raised throughout time, and there have been reports of penicillin-resistant strains of Streptococcus pneumoniae.

Although the clinical consequences of pneumococcal pneumonia produced by nonsusceptible and susceptible strains are not dissimilar, the use of penicillin as a treatment option is declining. CLSI distinguishes between meningitis and non-meningitis syndromes and classifies MIC breakpoints based on the route of penicillin administration (i.e., parenteral vs. oral route). Aside from drug absorption, distribution to the site of action is a pharmacokinetic characteristic that directly impacts treatment success. Penicillin resistance is reduced when the CLSI breakpoint is changed.

In recent years, bacteria have emerged as the primary cause of the onset of illnesses, indicating a reduction in the quality of human health. According to a study, Streptococcus pneumoniae is one of the bacteria that cause many of these illnesses (8).

Streptococcus pneumoniae is classified into many kinds depending on its antibiotic resistance. As a result of this resistance, handling germs becomes more challenging, and the options for therapy become restricted, lowering the quality of treatment and healthcare. Streptococcus pneumoniae was initially solely resistant to penicillin antibiotics. However, as time passes, these bacteria's resistance spreads and manifests in numerous forms, including resistance to macrolides, lincosamides, fluoroquinolones, tetracyclines, and sulfamethoxazole-trimethoprim (See Table 1) (8).

β-lactams are antibiotics responsible for inhibiting cell wall synthesis through binding to specific enzymes called Penicillin Binding Proteins (PBP) (9). Over time, the resistance level to different antimicrobial agents in Streptococcus pneumoniae increased and became a global problem. The prevalence of carrier-resistant strains has also expanded, exacerbating the problem. In addition, Streptococcus pneumoniae has intrinsic resistance to a wide range of antibiotics, including polypeptides, aminoglycosides, and first-generation quinolones (8).

β-lactam is a hydrophilic component that can enter the bacterial cell via the outer membrane's porin

channels. β-lactams work by binding to penicillin-binding protein (PBP)-trans-carboxypeptidase, an enzyme involved in the production of the peptidoglycan chain of the bacterial inner membrane. PBP interaction with β-lactam antibiotics leads to peptidoglycan production inhibition, cell division halt, and cell death. The interaction of β-lactams with the active site of PBP is strongly influenced by its structure. As a result, the presence of the β-lactam ring is critical in antibiotic and antibacterial action. When β-lactam engages with PBP, an enzyme-acyl complex is produced, and the C-N bonds in the four β-lactam rings are broken (14).

Table 1. Prevalence and resistance mechanisms of Streptococcus pneumoniae to certain antibiotics.

Class	Prevalence	Resistant Mechanism	MIC	Ref(s)
β-lactam	***Penisilin***			
	Penisilin: 35 %	Modification of penicillin-binding proteins	1 ppm	(8, 9)
	Oxacillin : 52 %	Modification of penicillin-binding proteins	4 ppm	(8, 9)
	Cefalophorines			
	Cefuroxime: 29,9%	Modification of penicillin-binding proteins	>4 ppm	(8-11)
	Ceftriaxone: 0-1%	Modification of penicillin-binding proteins	2 ppm	(8-10)
	Ceftaroline: 0-1%	Modification of penicillin-binding proteins	-	(8, 10, 12)
	Imipenem: 23.4%	Modification of penicillin-binding proteins	1 ppm	(8, 12)
Macrolides	20-40% Vancomycin: Erythromycin:	Mutations occur in the ribosomal RNA (rRNA) binding site for the macrolide antibiotic	 1 ppm >256 ppm	(8, 10, 12, 13)
Lincosamide	21.80%	Modification of the ribosome binding site through mutations in the 23S rRNA gene	-	(8)
Fluoroquinolones	1-2% Levofloxacin: Moxifloxacin:	Fluoroquinolones target bacterial DNA gyrase and topoisomerase IV, enzymes in DNA replication and repair. Mutations in the genes encoding these enzymes can reduce the binding affinity of the antibiotic to its target site, making it less effective.	 2 ppm 1 ppm	(8, 10)
Tetracycline	36.8 %	The ribosomal protection protein mechanism is more specific to tetracycline resistance.	>8 ppm	(8-10)
Trimethoprim-sulfamethoxazole	29.7 %	Trimethoprim-sulfamethoxazole works by targeting two different enzymes involved in the folate synthesis pathway, and mutations in these enzymes can reduce the binding affinity of the antibiotics, causing resistance.	>4 ppm	(8, 10, 12)

The resistance mechanism to β-lactams are as follows: (i) synthesis of β-lactamases that can damage β-lactams; (ii) decrease in permeability of the bacterial outer membrane causes a decrease in porin expression; (iii) changes in PBP structure; and (iv) active release of β-lactams from the bacterial cell (efflux system). β-lactamase production is thought to be a primary mechanism in developing clinically significant resistance to β-lactam in gram-negative bacteria. Genetic mutations result in substituting numerous amino acids in the protein sequence, affecting the structure of enzymes capable of hydrolyzing different antibiotics. Mutations might occur quickly as the microorganism grows resistant to antibiotics after therapy (14). The primary mechanism of β-lactam resistance in Streptococcus pneumonia is a recombination of the PBP gene acquired from similar species (such as Streptococcus mitis and Streptococcus oralis) (9). The low degree of penicillin resistance might be mainly attributed to alterations in PBP2x and -2b, resulting in non-penicillin-susceptible Streptococcus pneumonia (PNSP). However, a high resistance level can only be achieved by combining three PBP changes PBP1a, -2b, and -2x. An illustration showing the mechanism of β-lactam resistance can be seen in Figure 1.

Since Streptococcus pneumoniae is a facultative anaerobic bacterium, the electron transport chain is incomplete, conferring a low level of natural resistance

to several antibiotics (see Table 2). There are six PBPs in Streptococcus pneumonia, only three of which are associated with antibiotics resistance: PBP1a, PBP2x, and PBP2b.

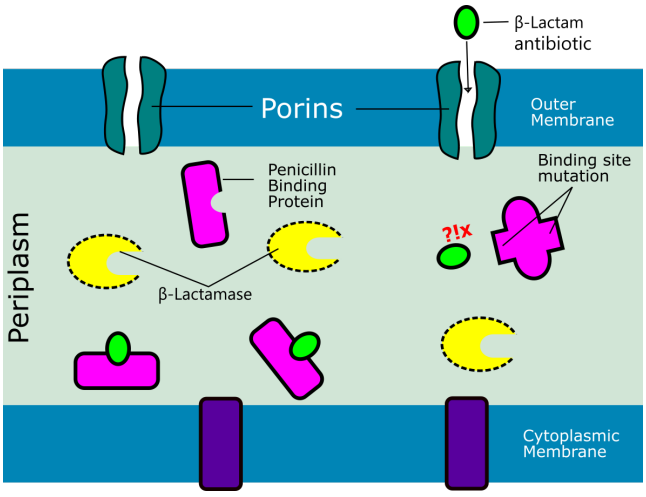

Figure 1. Mechanism of beta-lactam antibiotic resistance by mutation of penicillin-binding proteins (PBPs). This illustration was created inspired by the work of Gian MR. et al. (15).

Table 2. Relation of protein mutation in Streptococcus pneumoniae and β-lactams.

PBP	Mutation	Resistant Antibiotics
PBP2x	Thr550Ala	Cefotaxime
	T338A	Penicillin
PBP2b	Thr446Ala	Piperacillin
	T451A	Penicillin
PBP1a	Mosaic gene	Penicillin and cephalosporin
cp0A	Gly12Val	Piperacillin
ciaH	Thr230Pro	Cefotaxime
	Ala203Val	-
MurM	Mosaic gene	Penicillin and cephalosporin

Mouz N. et al. (1999) reported that it has been shown that positions 338 and 571 are important determinants for Streptococcus pneumoniae resistance to beta-lactam antibiotics (16). Among a series of 25 PBP2x sequences from clinical isolates, three contained T338A and Q552E mutations, and one showed a combination of T338A, Q552E, and S571P substitutions. The double mutant S-PBP2x*T338A, Q552E showed more than 90 and 80% decrease in acylation efficiency for cefotaxime and Pen G, respectively, compared to S-PBP2x. The T550A mutation occurs specifically because it causes high-level cefotaxime resistance and penicillin hypersensitivity simultaneously in the PBP2x mosaic gene or even as a single mutation in pbp2x from clinical isolates. The second substitution in the same codon, T550G, further increases cefotaxime resistance (17, 18). The 550A mutation leads to a 20-fold decrease in acylation efficiency for cefotaxime, possibly due to the deletion of hydrogen bonds between T550 and the carboxylate moiety attached to the six-membered ring of second and third-generation cephalosporins (16, 18).

In PBP 2b, the adjacent Thr446Ala with homolog Ser443SerAsn is a mutation that occurs with piperacillin and is described in all clinical isolates with low-affinity PBP 2b but differs from point mutations found in laboratory mutants. The mutated PBP 2b also significantly reduces the divisional response to piperacillin, indicating that this mutation is important in developing resistance in clinical isolates (16). The T446A amino acid substitution in PBP2b is known to reduce the binding affinity for penicillin by 60%, as seen in the study isolates with penicillin MIC >0.25 mg/mL (19).

Mutations in the penicillin-binding protein 1a (pbp1a) region increase the minimal inhibitory concentration (MICs) of penicillin and cefotaxime to >0.5 mg/mL, with substitutions at residues T371A and TSQF (574-577) NTGY being important for increasing penicillin resistance (20, 21). Another recent genome-wide association discovered 301 single-nucleotide polymorphisms, 73 of which induce amino acid alterations in cell wall production genes. Furthermore, the proteins MurM and MurN, expressed by the murMN operon, cause irregular cell wall formation by replacing linear muropeptides with atypically branched ones linked to penicillin resistance (22). Although MurM alone is insufficient to generate penicillin resistance, it is critical in achieving the greatest levels of penicillin and cephalosporin resistance.

Combating *Streptococcus pneumoniae* Resistance

Overcoming resistance to Streptococcus pneumoniae is a major challenge in treating infectious diseases. One approach to address this issue is the development of new antibiotics with more potent inhibitory activity against S. pneumoniae. In the last five years, the FDA has approved several new antibiotics for treating S. pneumoniae infections, including Omadacycline, Lefamulin, Eravacycline, Delafloxacin, Plazomicin, and Cefiderocol. Omadacycline and Lefamulin are tetracycline and pleuromutilin antibiotics effective in treating pneumonia and skin and soft tissue infections caused by S. pneumoniae resistant to other antibiotics (23-25). Eravacycline, a newer generation tetracycline antibiotic, is approved for treating intra-abdominal and urinary tract infections caused by antibiotic-resistant bacteria, including S. pneumoniae (26, 27). Delafloxacin is a new fluoroquinolone antibiotic effective in treating skin and soft tissue infections caused by S. pneumoniae (28). Plazomicin is a new aminoglycoside antibiotic approved for treating urinary

tract infections caused by antibiotic-resistant bacteria, including S. pneumoniae (29). Cefiderocol, a third-generation cephalosporin antibiotic, is approved for treating difficult-to-treat infections caused by antibiotic-resistant bacteria, including S. pneumoniae (30). Proper use of antibiotics can help slow the development of antibiotic resistance and maintain the effectiveness of these drugs in treating infectious diseases in the future.

Vaccination represents a crucial aspect of the efforts to prevent Streptococcus pneumoniae infections. Vaccines have been proven to significantly reduce the incidence of infections caused by S. pneumoniae, which can lead to a decreased likelihood of the emergence of resistant strains. Three types of pneumococcal vaccines are currently available, including pneumococcal polysaccharide vaccine (PPV), pneumococcal conjugate vaccine (PCV), and pneumococcal polysaccharide-conjugate vaccine (PCV-P) (31, 32). PCV and PCV-P vaccines are designed to elicit a better immune response than PPV. PCV vaccines are available in various formulations, depending on the number of pneumococcal serotypes captured in the vaccine (33). PCV13 is widely used in high-risk children and adults, while PCV10 is used in some countries (34, 35). Studies have shown that the use of pneumococcal conjugate vaccine has significantly reduced the number of pneumococcal infections, including infections caused by serotypes included in the vaccine (36, 37). In children, PCV13 has been demonstrated to be effective in reducing the incidence of pneumococcal invasive and non-invasive diseases, such as pneumonia, otitis media, and meningitis (38). In countries that have introduced the PCV vaccine in national immunization programs, a significant decrease has been observed in the incidence of pneumococcal infections and antibiotic resistance of the bacteria (39). However, pneumococcal vaccines do not guarantee protection from all pneumococcal serotypes (40, 41), and developing more effective and comprehensive vaccines remains a research goal.

The inappropriate use of antibiotics is a major driver of antibiotic resistance, including S. pneumoniae resistance. Overuse and misuse of antibiotics can lead to resistance, making infections more difficult to treat (42). Therefore, antibiotic stewardship is critical for preventing and controlling antibiotic resistance (43). Various steps have been taken to implement antibiotic stewardship programs to address the issue of antibiotic resistance. These include educating healthcare providers and patients on the appropriate use of antibiotics, promoting guidelines and best practices for prescribing antibiotics, and establishing surveillance systems to monitor the emergence of antibiotic resistance (44-47). Additionally, various regulations and policies have been implemented to encourage the appropriate use of antibiotics, such as guidelines for the appropriate use of antibiotics in different settings, restrictions on the use of certain antibiotics, and requirements for reporting antibiotic use and resistance data (48). One example of a policy that promotes antibiotic stewardship is the CDC's Core Elements of Hospital Antibiotic Stewardship Programs, which provides a framework for healthcare facilities to develop and implement effective antibiotic stewardship programs (49). Similarly, the World Health Organization (WHO) has developed a global action plan to combat antimicrobial resistance, which includes measures to promote the appropriate use of antibiotics and support the development of new antibiotics (50).

Author Perspective

Our mini-review highlights the critical role of penicillin-binding proteins (PBPs) mutations in the emergence and spread of antibiotic resistance in Streptococcus pneumoniae, particularly in the context of β-lactam antibiotics. Although several mechanisms of β-lactam resistance have been identified, including altered expression of efflux pumps and β-lactamases, PBPs mutations remain a major driver of resistance in this pathogen. However, much remains to be learned about the precise nature of these mutations and how they interact with other genetic and environmental factors to shape the evolution of resistance. Further research is needed to fully understand the underlying mechanisms of PBPs mutations and how they contribute to the development of resistance. Moreover, there is a need to explore novel strategies for combating antibiotic resistance in this pathogen, particularly those that target the PBPs mutations. There are several efforts have been proposed to overcome this issue. To combat resistance, novel strategies such as targeting alternative penicillin-binding proteins (51), utilizing combination therapies (52-54), and targeting biofilm formation have been proposed (55). Furthermore, alternative treatments such as vaccines, bacteriophages, and probiotics could provide a promising alternative to traditional antibiotics (56). The development of new antimicrobial agents and approaches, combined with efforts to minimize the inappropriate use of antibiotics, will be crucial in the fight against antibiotic resistance in S. pneumoniae and other bacterial pathogens. It is important to recognize that antibiotic resistance is a global issue requiring coordinated effort across the scientific, medical, and public health communities.

Conclusion

Changes in Penicillin Binding Proteins involved in the production of the cell wall of Streptococcus Pneumonia bacteria are the key factor in the emergence of antibiotic resistance, especially for β-lactam antibiotics where mutations lead to resistance in PBP1a, PBP2x,

and PBP2b. The development of resistance to β-lactam antibiotics is a complex mechanism that mutations can influence in other PBP and non-PBP genes. However, the main limitation of the review is that substitutions outside the specific area of PBP genes were not examined, which may also contribute to resistance and other mechanisms.

In conclusion, understanding the underlying mechanisms of PBPs mutations and their contribution to antibiotic resistance in S. pneumoniae is crucial to developing novel strategies to combat this issue. While combining new β-lactam antibiotics with novel β-lactamase inhibitors and targeting PBP3 with new antibiotics have been proposed as effective ways to overcome resistance, alternative treatments like vaccines, bacteriophages, and probiotics may provide a promising alternative to traditional antibiotics. Additionally, combining different antibiotics or antibiotic classes and targeting biofilm formation may be effective ways to enhance the efficacy of antibiotics and overcome resistance. Further research is needed to develop effective therapies against S. pneumoniae infections.

Declarations

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Conflict of Interest

The authors declare no conflicting interest.

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